



1623

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
(Case No. 00-1206-B)

In the Application of:

Alex Burgin, et al

Application No.: 09/993,245

Filing Date: November 14, 2001

For: Structures and Methods for Designing  
Topoisomerase I Inhibitors

Examiner: TBA

Group Art Unit: 1623

Confirmation No. 7743

Commissioner of Patents and Trademarks  
Washington, DC 20231

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1. We are transmitting herewith the attached:

- a) Supplemental Information Disclosure Statement
- b) U.S. PTO 1449 form with copies of 30 references
- c) Return Receipt Postcard

2. With respect to additional fees:

No Additional Fee is Required.

3. GENERAL AUTHORIZATION: Please charge any additional fees or credit overpayment to Deposit Account No. 13-2490. A duplicate copy of this sheet is enclosed.

4. CERTIFICATE OF MAILING UNDER 37 CFR § 1.8: The undersigned hereby certifies that this Transmittal Letter and the paper, as described in paragraph 1 hereinabove, are being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents and Trademarks, Washington, D.C. 20231 on this 14 day of November, 2002.

Dated: 11/14/02

By: [Signature]

Emily Miao  
Reg. No. 35,285

McDONNELL BOEHNEN HULBERT & BERGHOFF  
300 South Wacker Drive  
Chicago, Illinois 60606  
Telephone (312) 913-0001; Fax (312) 913-0002



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Sir:

In order to comply with discretionary regulations 37 CFR §§1.97 and 1.98, attached hereto is Form PTO-1449, copies<sup>1</sup> of the documents listed thereon. These documents contain information which the Examiner may consider to be important in deciding whether to allow the present application to issue as a patent.

1. Boehm, et al., U.S. Patent No. 5,004,758, issued 04/02/91
2. Earnshaw, et al., U.S. Patent No. 5,070,192, issued 12/03/91
3. Wilson, et al., U.S. Patent No. 5,856,116, issued 01/05/99
4. International Patent No. WO 99/45379 published 09/10/99
5. International Patent No. WO 00/14105 published 03/16/00

<sup>1</sup>To the extent that a document is listed and no copy of same is attached, then such document is not at the present time available to the undersigned or is available in the file of a parent application. If a listed document is not in the English language and an English translation is readily available, such translation is also attached; if translation is not attached it is not readily available to the undersigned. If a foreign language patent document is cited, and an English language equivalent is known to the undersigned, then such equivalent patent is also cited on the attached form along with the corresponding foreign language patent and a connecting arrow indicated therebetween; if no such English language equivalent is cited, then none is known to undersigned.

6. Burgin A., et al., "A novel suicide substrate for DNA topoisomerases and site-specific recombinases," *Nucleic Acids Res.*, Volume 23, pp. 2973-2979 (1995)
7. Champoux J., et al., "DNA Topoisomerases: structure, function, and mechanism," *Ann. Rev. Biochem.*, Volume 70, pp. 369-413 (2001)
8. Chen A., et al., "DNA topoisomerases: Essential enzymes and lethal targets," *Rev. Pharmacol. Toxicol.*, Volume 34, pp. 191-218 (1994)
9. Chourpa, I., et al., "Modulation in kinetics of lactone ring hydrolysis of camptothecins upon interaction with topoisomerase I cleavage sites on DNA," *Biochem.*, Volume 37, pp. 7284-7291 (1998)
10. Cushman, M., et al., "Synthesis of new indeno[1,2-c]isoquinolines: cytotoxic non-camptothecin topoisomerase I inhibitors," *J Med Chem*, Volume 5, pp. 3688-3698 (2000).
11. D'Arpa P., et al., "cDNA cloning of human DNA topoisomerase I: catalytic activity of a 67.7-kDa carboxyl-terminal fragment," *Proc Natl. Acad. Sci USA*, Volume 85, p. 2543-2547 (1988)
12. Fertala, J., et al., "Substitutions of Asn-726 in the active site of yeast DNA topoisomerase I define novel mechanisms of stabilizing the covalent enzyme-DNA intermediate," *J. Biol. Chem*, Volume 275, pp. 15246-15253 (2000).
13. Fiorani, P., et al., "Domain interactions affecting human DNA topoisomerase I catalysis and camptothecin sensitivity," *Mol Pharmacol*, Volume 56, pp. 1105-1115 (1999).
14. Giovanella, B. C., et al., "DNA topoisomerase I--targeted chemotherapy of human colon cancer in xenografts," *Science*, Volume 246, pp. 1046-8 (1989)
15. Hertzberg, R. P., et al., "On the mechanism of topoisomerase I inhibition by camptothecin: evidence for binding to an enzyme-DNA complex," *Biochem.*, Volume 28, pp. 4629-4638 (1989)
16. Hsiang, Y. H., et al., "Camptothecin induces protein-linked DNA breaks via mammalian DNA topoisomerase I," *J. Biol. Chem.*, Volume 260, pp. 14873-14878 (1985).
17. Hsiang, Y. H., et al., "DNA topoisomerase I-mediated DNA cleavage and cytotoxicity of camptothecin analogues," *Cancer Res*, Volume 49, p. 4385-9 (1989).
18. Kehr, D. F. S., et al., "Modulation of camptothecin analogs in the treatment of cancer: a review," *Anti-Cancer Drugs*, Volume 12, pp. 89-105 (2001)

19. Krogh, B. O., Shuman, S., "Catalytic mechanism of DNA topoisomerase IB," *Mol. Cell*, Volume 5, pp. 1034-1041 (2000).
20. Li, X. G., et al., "Involvement of amino acids 361 to 364 of human topoisomerase I in camptothecin resistance and enzyme catalysis," *Biochem. Pharmacol.*, Volume 53, pp. 1019-1027 (1997).
21. Nitiss, J. L. and Wang, J. C., "DNA topoisomerase-targeting antitumor drugs can be studied in yeast," *Proc. Natl. Acad. Sci. U.S.A.*, Volume 85, pp. 7501-7505 (1988)
22. Redinbo, M. R., et al., "Crystal structures of human topoisomerase I in covalent and noncovalent complexes with DNA," *Science*, Volume 279, pp. 1504-1513 (1998)
23. Rubin, E., et al., "Identification of a mutant human topoisomerase I with intact catalytic activity and resistance to 9-nitro-camptothecin," *J Biol Chem*, Volume 269, pp. 2433-2439 (1994)
24. Stewart, L., et al., "A functional linker in human topoisomerase I is required for maximum sensitivity to camptothecin in a DNA relaxation assay," *J. Biol. Chem.*, Volume 274, pp. 32950-32960 (1999)
25. Stewart, L., et al., "A model for the mechanism of human topoisomerase I," *Science*, Volume 279, pp. 1534-1541 (1998)
26. Stewart, L., et al., "Biochemical and biophysical analyses of recombinant forms of human topoisomerase I," *J. Biol. Chem.*, Volume 271, pp. 7593-7601 (1996).
27. Stewart, L., et al., "Biochemical and biophysical analyses of recombinant forms of human topoisomerase I," *J. Biol. Chem.*, Volume 269, pp. 355-372 (1997)
28. Strumberg, D., et al., "Synthesis of cytotoxic indenoisoquinoline topoisomerase I poisons," *J Med Chem*, Volume 11, pp. 446-457 (1999)
29. Smith, J. L., Hendrickson, W. A., Honzatko, R. B., Sheriff, S., "Structural heterogeneity in protein crystals," *Biochem.*, Volume 25, pp. 5018-5027 (1986)
30. Tamura, H., et al., "Molecular cloning of a cDNA of a camptothecin-resistant human DNA topoisomerase I and identification of mutation sites," *Nucleic Acids Res.*, Volume 19, pp. 69-75 (1991).

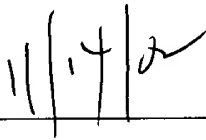
In accordance with MPEP Sections 609 and 707.05(b), it is requested that each document cited (including any cited in applicant's specification which is not repeated on the attached Form PTO-1449) be given thorough consideration and that it be cited of record in the prosecution history of the

present application by initialing on Form PTO-1449. Such initialing is requested even if the Examiner does not consider a cited document to be sufficiently pertinent to use in a rejection, or otherwise does not consider it to be prior art for any reason, or even if the Examiner does not believe that the guidelines for citation have been fully complied with. This is requested so that each document becomes listed on the face of the patent issuing on the present application.

The present Disclosure Statement is being submitted in compliance with 37 CFR 1.56 insofar as an Examiner might consider any of the cited documents important in deciding whether to allow the application to issue as a patent, but the citation of each document is not to be construed as an admission that such document is necessarily relevant or prior art. No representation is intended that the cited documents represent the results of a complete search, and it is anticipated that the Examiner, in the normal course of examination, will make an independent search and will determine the best prior art consistent with 37 CFR 1.104(a) and 1.106(b) and, in the course of each search, will review for relevance every document cited on the attached form even if not initialed.

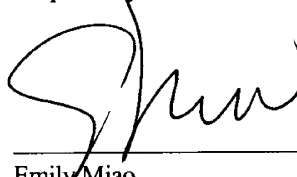
Early and favorable consideration is earnestly solicited.

Dated: \_\_\_\_\_



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Telephone: (312) 913-0001  
Facsimile: (312) 913-0002

Respectfully submitted,



Emily Miao  
Registration No. 35,285

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## U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date
	1.	5,004,758	04/02/91	Boehm, et al.	514	283	11/02/88
	2.	5,070,192	12/03/91	Earnshaw, et al.	536	27	03/23/88
	3.	5,856,116	01/05/99	Wilson, et al.	435	23	05/25/95

## FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation Yes No
	4.	WO 99/45379 -	09/10/99	PCT			
	5.	WO 00/14105 -	03/16/00	PCT			

## OTHER DOCUMENTS - Including Author, Title, Date, Pertinent Pages, Etc.

6.	Burgin Jr., A. B., et al., "A novel suicide substrate for DNA topoisomerases and site-specific recombinases," <i>Nucleic Acids Res.</i> , Volume 23, pp. 2973-2979 (1995). —
7.	Champoux, J. J., "DNA Topoisomerases: structure, function, and mechanism," <i>Ann. Rev. Biochem.</i> , Volume 70, pp. 369-413 (2001).
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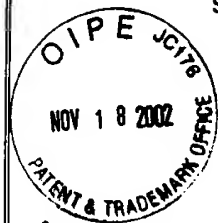
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